Glutethimide—A New Nonbarbiturate Hypnotic

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• **A new anticonvulsant, nonbarbiturate compound, Doriden (ethyl-a-phenyl-glutarimide) was studied for clinical activity as a hypnotic drug in mildly disturbed patients on the acute Psychiatric Service of Los Angeles County General Hospital. It was found to have approximately the same hypnotic activity as pentobarbital in the dosages recommended (1 gm. Doriden=200 mg. pentobarbital).**

BECAUSE PREVIOUS INVESTIGATIONS with a new anticonvulsant, nonbarbiturate compound, glutethimide (Doriden®), which chemically is ethyl-a-phenyl-glutarimide, showed that it depressed the central and autonomic nervous systems, question arose as to whether it might not also be active as an hypnotic. A study was made to find out.

Observations were made on two series of mildly disturbed, transient inpatients who were in the care of the Psychiatric Service of Los Angeles County General Hospital. Each series was composed of patients who requested a "sleeping pill" but who were not clinically in any serious need of sedation. In the first series, patients were given Doriden, 0.5 gm., or pentobarbital, 0.09 gm., or a placebo—presumably according to random selection. After completion of the study it was learned that members of the nursing staff, aware of the nature of each pill, had sometimes selected patients for the placebo who wanted a "sleeping pill" but appeared in little or no need of one, and that they had also sometimes given an "active" drug if the patient seemed upset or fretful. In the second series, the nurses could not identify the placebo and the patients were randomly distributed into the three groups. In the second series the two drugs were given in twice the dose used in the first series. A total of 175 patients received the drug on one or more occasions.

All patients on the Psychiatric Service are confined at night and are observed at regular hourly intervals by the nursing staff. In this study a careful record was kept by the nurse of whether the patient appeared to be awake at each of eight observation periods at hourly intervals.

RESULTS

Comparison of the control (placebo) groups of the two series shows that the controls of Series 1 were considered to be asleep on a significantly larger number of occasions than the controls of Series 2, the means being respectively 7.02 and 6.51 (t=3.4, p=less than .01). This is consistent with the biased selection of patients for the placebo group of Series 1, and suggests two things: (1) the placebo group in Series 1 is in no sense a "control" for the treated groups in this series, and (2) the bias favoring sleep in the placebo group also favors wakefulness in the treated groups of Series 1.

It was therefore felt that the treated groups in Series 1 might be compared with the placebo group in Series 2, but that the bias affecting the former would tend to prejudice reports as to the hypnotic effect of either of the drugs used.

The reported effect (Series 1) of Doriden, 0.5 gm., did not differ significantly from that of pentobarbital, 0.09 gm., nor was there a significant difference between them in twice that dosage (Series 2). The conditions associated with both drugs in both series did significantly differ from the conditions associated with Series 2 controls (t values ranging from 2.3 to 6.0 for the eight differences between these four treatment groups and the control group at the two times shown in Table 1).

The differences between Doriden and pentobarbital in Series 1 and in Series 2 were trivial and not significant (t values ranged from 0.2 to 1.0).

With respect to the increased sleep with increased dosage (Series 1 compared with Series 2), it must

TABLE 1.—*Results in the Eight-hour Period and in the First Five Hours, Showing Number of Intervals at which Patient Appeared Asleep*

Treatment Series	Number of Patient-Nights	Eight Hours		First Five Hours	
		Average	$V_{\bar{x}}$*	Average	$V_{\bar{x}}$*
Placebo (2nd series)	129	6.51	.0139	3.95	.0074
Pentobarbital (0.09 gm.)	209	6.93	.0091	4.22	.0065
Pentobarbital (0.18 gm.)	58	7.38	.0206	4.67	.0069
Doriden (0.5 gm.)	340	6.95	.0051	4.33	.0051
Doriden (1 gm.)	56	7.29	.0198	4.57	.0084

* $V_{\bar{x}} = \frac{\Sigma (x - \bar{x})^2}{n (n - 1)}$, where $V_{\bar{x}}$ is variance of the mean, x is the number of intervals recorded as asleep, $\bar{x}$ is the mean, and n the number of patient-nights.

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Ciba Pharmaceutical Products, Inc., supplied the Doriden used in this study.

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be noted again that the treatment groups in Series 1 were biased in favor of wakefulness. The differences observed, while statistically significant, cannot therefore be clearly attributed to dosage rather than to bias, although it would be reasonable to expect dosage-response relations of the general kind observed.

With respect to side effects, one patient complained of excessive sleepiness the afternoon following his fourth night on Doriden (0.5 gm. each evening), and in one patient jaundice of unknown cause developed; it cleared spontaneouly in eight days.

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